

KATA PENGANTAR

Dengan penuh rasa syukur kehadiran Allah SWT, Media Farmasi Vol. 12 No. 1 Tahun 2015 telah terbit.

Pada edisi ini, Jurnal Media Farmasi menyajikan 11 artikel yang kesemuanya merupakan hasil penelitian. Enam artikel dari luar Fakultas Farmasi UAD membahas, (1) Formulasi dan evaluasi masker wajah *peel-off* yang mengandung kuersetin (2) Pengaruh polivinil pirolidon (PVP) dalam absorpsi piroksikam (3) Uji perbandingan aktivitas antijamur *Pityrosporum ovale* dari kombinasi ekstrak etanol buah belimbing wuluh dan daun sirih (4) Aktivitas inhibisi α -amilase ekstrak karagenan dan senyawa polifenol (5) Uji antihipertensi infus kombinasi biji dan rambut jagung (6) Layanan pesan singkat pengingat meningkatkan kepatuhan minum obat. Lima artikel dari peneliti Fakultas Farmasi UAD yang membahas tentang : (1) Formulasi emulgel minyak biji bunga matahari (2) Aktivitas antifungi fraksi etil asetat ekstrak daun pacar kuku (3) Karakteristik genetik *Actinomyces* (4) Simvastatin sebagai hepatoprotektor (5) Faktor yang diprediksi berpengaruh terhadap pengobatan sendiri.

Harapan kami, jurnal ini dapat bermanfaat bagi pembaca atau menjadi referensi peneliti lain. Kritik dan saran membangun, senantiasa kami terima dengan tangan terbuka.

Dewan Editor

THE INFLUENCE OF POLYVINYL PYRROLIDONE (PVP) ON PIROXICAM ABSORPTION WITH EVERTED INTESTINAL SAC METHOD

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ABSTRACT

Oral drug absorption was highly influenced by dissolution rate, especially for poorly and insoluble drugs. Piroxicam is a nonsteroidal anti-inflammatory drug that is practically insoluble in water. The oral absorption rate of piroxicam is dependent on its dissolution rate in the GI tract. Polyvinyl Pyrrolidone (PVP) as surfactant can increase drug solubility by means of a micelle forming mechanism. The aim of the study was to know the influence of addition and variation of Polyvinyl Pyrrolidone (PVP) on Piroxicam absorption with everted intestinal sac method. The concentration of piroxicam solution was prepared by PVP in 1.0, 2.0 and 3.0 % respectively. Crane and Wilson tube containing 75 ml of the mucosal fluid was taken at 37°C in waterbath. Then, serosal solution of 1.5 ml was added to intestinal sac by turned upside down and tied to a cannula, then put into the tube containing the mucosal fluid and constantly flowing oxygen gas. Serosal solution of 1 ml were taken every 15 minutes and then diluted with 2 ml of Ba (OH) 2 and 2 ml of ZnSO4 then centrifuge until 25 minute. The absorbant of supernatant was measured by UV spectrophotometer and data analyse was calculated by one-way ANAVA. PVP at 1%,2% and 3% increased piroxicam absorption from the phosphate buffer pH 7.5 compared with negative control. According to P_{app} , the values were 2.52 ± 0.43 cm/minute (negative control), 3.41 ± 2.17 cm/minute (1% PVP), 2.75 ± 1.14 cm/minute (2% PVP) and 4.77 ± 4.93 cm/minute (3% PVP) respectively. In conclusion. Lower doses of the surfactant (1%, 2%, and 3% PVP) significantly increased absorption of the drug by altering the membrane permeability.

Keywords: Piroxicam, absorption, in vitro, PVP

INTRODUCTION

Physicochemical of drug, anatomy and physiology function of drug absorption are important to determine of the drug concentration in the body. It is important to make certain about formulation and evaluation of medicinal products (Shargel and Yu, 1999).

Piroxicam is one of nonsteroidal anti-inflammatory drug that used to relieve the symptoms of osteoarthritis and rheumatoid arthritis. It has activity to inhibited prostaglandin synthesis by cyclooxygenase pathway, inhibited chemotaxis and influence of liposomal enzymes release (Gennaro, 1990). It has good absorption in the gastrointestinal tract but very poorly soluble in water. The methods to increase the solubility of drugs such as change the drug molecules, modification with adjuvant that can improve the solubility of the drug (Lund, 1994).

Adjuvant is one of substance that can be increasing the solubility

of drug in water. This study is observing the solubility of piroksikam after treatment with PVP as an adjuvant. The characteristic of PVP is soluble in water, hygroscopic and inert that used as a binder (Anonymous, 2007). Several studies reported that PVP is able to increase the solubility of Pentagamavunon-0 (Fauzia, 2004). PVP also indicated can increase the absorption of Pentagamavunon-0 by in vitro studies (Farmawati, 2004). Complex formation from PGV-0 indicated as concentration of PGV-0 that are absorbed in the jejunum and ileum on rat (Wahyuningsih, 2003).

Based on the recent study, this research was do to observe the influence after addition with Polyvinyl Pyrrolidone (PVP) on Piroxicam by dependent manner and also to observe the small intestine area which have optimal absorption in the case of active transport. This method was simple and reproducible to distinguish the active and passive absorption.

MATERIALS AND METHODS

Materials

Male Wistar rats weighing 170-250 grams from the Faculty of Veterinary Medicine, Gadjah Mada University, piroxicam (Nantong General Pharmaceutical Factory), PVP (E. Merck), ether (technical degree), sodium dihydrogen phosphate p.a (E. Merck), disodium hydrogen phosphate p.a (E. Merck), sodium chloride p.a (E. Merck), barium hydroxide p.a (E. Merck), zinc sulfate p.a (E. Merck), oxygen gases, and aquadestilata.

Instrument

Crane and Wilson tube were modified by Yuwono from *Bandung Technology Institute* (ITB), Genesys 10 Spectrophotometer, Analytical balance (Shimadzu Scientific Ltd.), Centrifuges MLW T51.1, Sonicator Elma T 570, Digital pH meter Omega models 5003, Waterbath (Shimadzu Scientific Ltd.), tools for surgery, glassware, volume pipette, test tube and flask.

Preparation

Making of isotonic phosphate buffers solution (pH 7.4)

Mix the 1.6 grams of sodium dihydrogen phosphate, 11.976 grams disodium hydrogen phosphate and 4.4 grams of sodium chloride on distilled water. Buffer solution is a substance that can resist changes in pH when small amounts added of acid or base (Martin et al, 1983).

Making of Piroxicam's Stock Solutions

100 mg of Piroxicam put in 500.0 ml flask, dissolved in a sonicator, then added phosphate buffer pH 7.4 to mark boundaries.

Making of PVP concentration

A number of PVP was taken into a 100 ml flask, then added a solution of phosphate buffer pH 7.4 up to the mark. PVP is made series levels are 1, 2, and 3% (w/v).

Determination of Maximum Wavelength

1.0 ml stock solution added to 4.0 ml PVP in phosphate buffer pH 7.4 at various levels. Thus, it was measured the absorbance at 200-400 nm. Blank solution used as much as 1.0 ml of solvent solution on pH 7.4

phosphate buffer added 4.0 ml PVP on phosphate buffer pH 7.4. The experiments were performed with a variety of PVP levels are 0, 1, 2, and 3% (w/v).

Determination of Raw curve.

Stock solution was prepared from concentration levels of 10, 12, 14, 16, 18 $\mu\text{g/ml}$, then takes 1.0 ml of each series dilution to 4.0 ml PVP (1% w/v) in phosphate buffer solution pH 7.4. The solution was measured at a wavelength of maximum absorbance. Blanko that used in the form of phosphate buffer pH 7.4 as much as 1.0 ml plus 4.0 ml PVP (1% w / v) in phosphate buffer solution pH 7.4. The experiment was repeated up to 3 times.

Permeability Test

Determination of the biological membranes permeability as absorption area was observe by in vitro study. It is using rat intestinal inverse method that done by some male mice were fasted during the first 20-24 hours. The mice were killed with ether, and his stomach was opened along the midline and intestines removed. Intestinal (length 15 cm below) the pylorus was

removed and 20 cm at the bottom is used for the experiment. The contents are cleaned with a solution of NaCl 0.9% w / v. Rat intestine was divided into 2 equal length, where the top is used for the experiment and the bottom is used as a control, then each piece of intestine behind the glass rod with a diameter of 2 mm and the rest of the remaining dirt is cleaned with sodium chloride 0.9% w / v (serosal fluid). Effective intestinal length used in this study is 7 cm long.

Mucosal fluids are made in the form of a solution with concentration of 20 mg piroxicam% in isotonic phosphate buffer pH 7.4 with PVP at level 1, 2, 3% (w / v), and is used as a negative control for comparison (without the addition of PVP) is then inserted into the tube. Tubes containing 75 ml of mucosal fluid put in a water bath at a temperature of 37°C . Serosal fluid, 1.5 ml incorporated into the intestinal sac that has been turned upside down and tied to the cannula, then inserted into the tube which already contains the mucosal fluid and constantly flowing O_2 gas at a rate of approximately 100

bubbles per minute. Oxygen gas is used to maintain the structure of the intestinal wall (Wahyuningsih, 2003). During the trial maintained that all parts of the intestinal mucosal submerged in the liquid. Samples were taken every 15 minutes until the 75th minute.

Serosal fluid's sample was taken from intestinal sac (1 ml) added 2 ml of zinc sulfate 5% (w / v) and 2 ml of 0.3 N barium hydroxide than centrifuged for 25 minutes. Supernatan was taken in tube and measured the absorbance by spectrofotometre UV-VIS.

Data Analysis

The cumulative amount absorbed piroxicam obtained from the calculation using the standard curve equation piroxicam, then made curve cumulative amount of piroxicam absorbed with time (before the steady state conditions). Curve cumulative amount of piroxicam absorbed with time after steady state was made taking into account the t_{lag} before steady state conditions. Absorption rate (K), membrane permeability (P), and the lag time is calculated from the

regression equation curve cumulative amount of piroxicam absorbed with time after steady state conditions in each replication.

The data obtained in the form of a cumulative amount absorbed piroxicam, constant speed of absorption, permeability, and the lag time at various levels of PVP were analyzed with the Kolmogorov-Smirnov test to determine the data were normally distributed or not (Daniel, 1999).

RESULT AND DISCUSSION

The result of absorption effect after addition PVP is doing by adding the mucosal solution. PVP content variation is added by 1; 2; and 3% (b/v) compared with a negative control (without addition of PVP). The concentration of piroxicam are classified based on the piroxicam solubility in water (0.01%). PVP concentration (1.0%) was sufficient to be above the solubility limit.

The results of in vitro studies show that the serosal's absorbance solution that containing piroxicam. It

was taken every 15 min. Samples were taken first in the 5th minutes, but the data shows the absorbance at the minute piroxicam absorbed amount is zero, so that the next replication sample measurements began in the 15th minute. The amount of absorbed piroxicam obtained from the calculation using the standard curve equation $y=0.0392x + 0.0712$.

PVP as a substance that can increase the solubility of drug. It was expected to increase the speed of drug absorption. The solubility was related with speed of drug absorption which has a linear curve. Drug absorption from the gastrointestinal tract into the blood generally occurs after it dissolved in the fluid of membrane surrounding the absorption site.

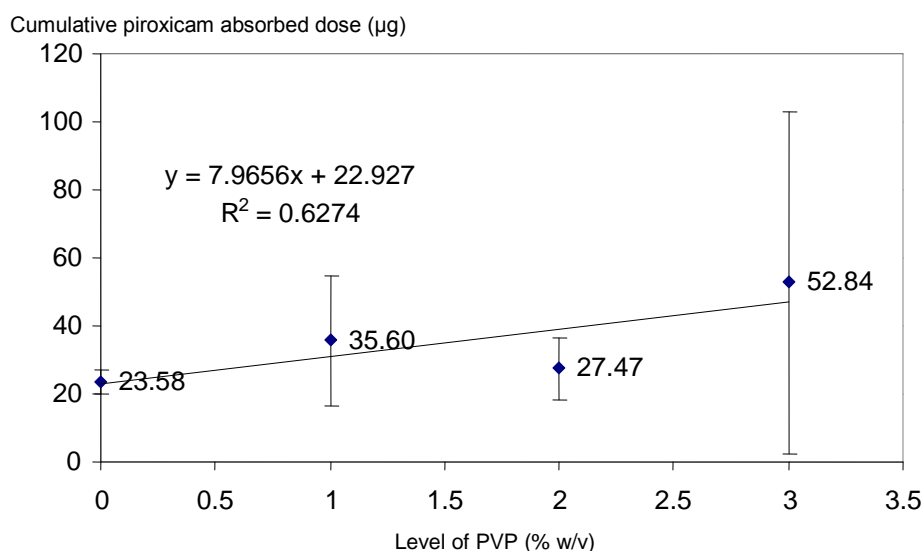


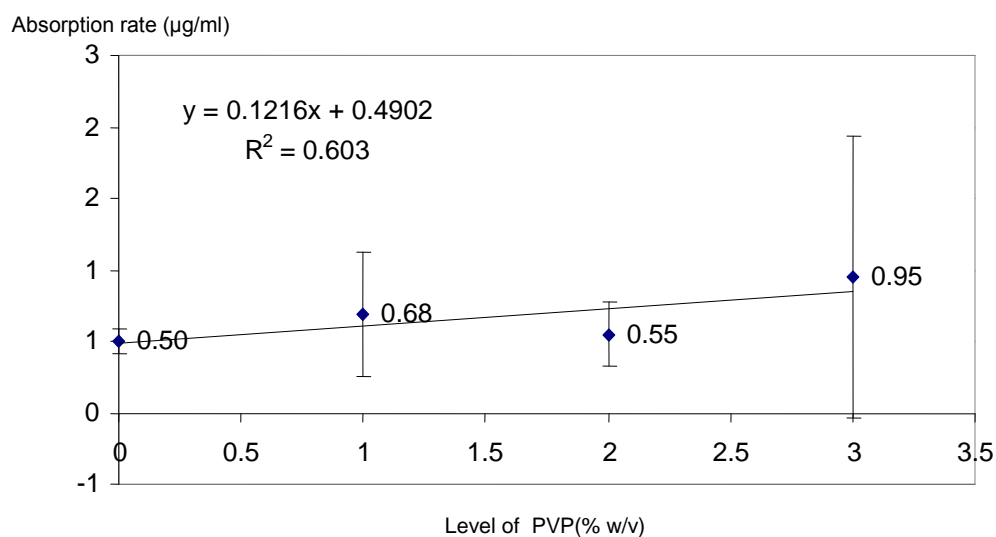
Figure 1. Relationship curve between levels of PVP with cumulative piroxicam absorbed dose

Table I. Total cumulative piroxicam absorbed dose on the addition of 1, 2, and 3% (w/v) PVP

Time (minute)	Negative control	PVP 1% (w/v)	PVP 2% (w/v)	PVP 3% (w/v)
15	0	0.37 ± 0.64	0	1.31 ± 1.99
30	1.44 ± 1.25	3.47 ± 3.04	1.89 ± 2.52	13.01 ± 8.44
45	5.48 ± 1.50	19.25 ± 7.39	8.29 ± 4.10	21.59 ± 19.70
60	14.69 ± 1.73	25.10 ± 10.82	13.99 ± 7.27	43.11 ± 42.69
75	23.58 ± 3.50	35.60 ± 18.94	27.47 ± 9.10	52.84 ± 50.33

Table II. Absorption rate (K), Membrane permeability (Pm), and the lag time on any variation of PVP concentration in the mucosal solution

Groups	Absorption rate (µg/minute)	Permeability (cm/minute)	Lag time (minutes)
Negative control	0.50 ± 0.09	2.52 ± 0.43	29.58 ± 4.47
PVP 1%	0.68 ± 0.43	3.41 ± 2.17	18.21 ± 8.83
PVP 2%	0.55 ± 0.23	2.75 ± 1.14	28.42 ± 7.19
PVP 3%	0.95 ± 0.99	4.77 ± 4.93	15.27 ± 4.52

**Figure 2.** Relationship curve between levels of PVP with absorption rate of piroxicam

Absorption rate (K), the permeability of the membrane (Pm), and the lag time is calculated from the regression equation that was derived from the cumulative amount of piroxicam curve absorbed with time after steady state conditions. Table II shows the calculation of piroxicam's flux, membrane

permeability, and the latent time related with increased levels of PVP that was added in mucosal fluids. From the calculation results can be seen that increasing PVP concentration used did not show any significant change in the value of K, Pm, or lag time.

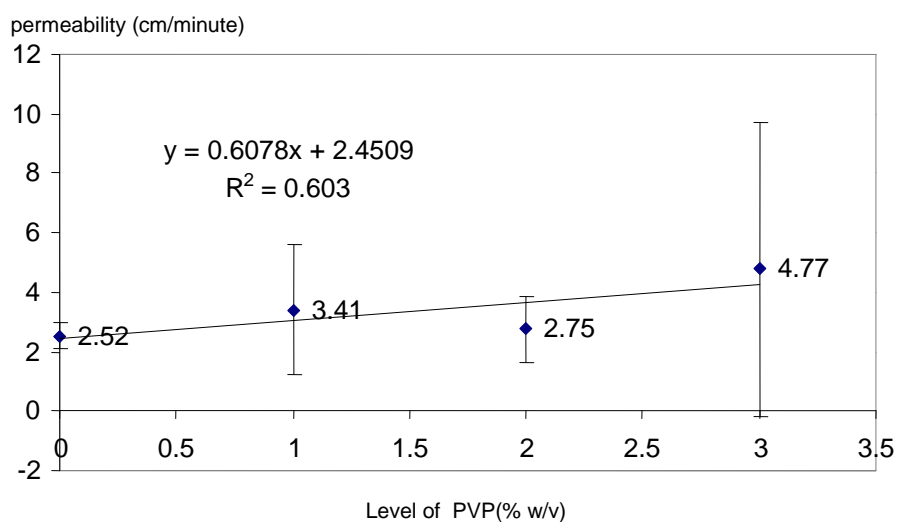


Figure 3. Relationship curve between levels of PVP with membrane permeability

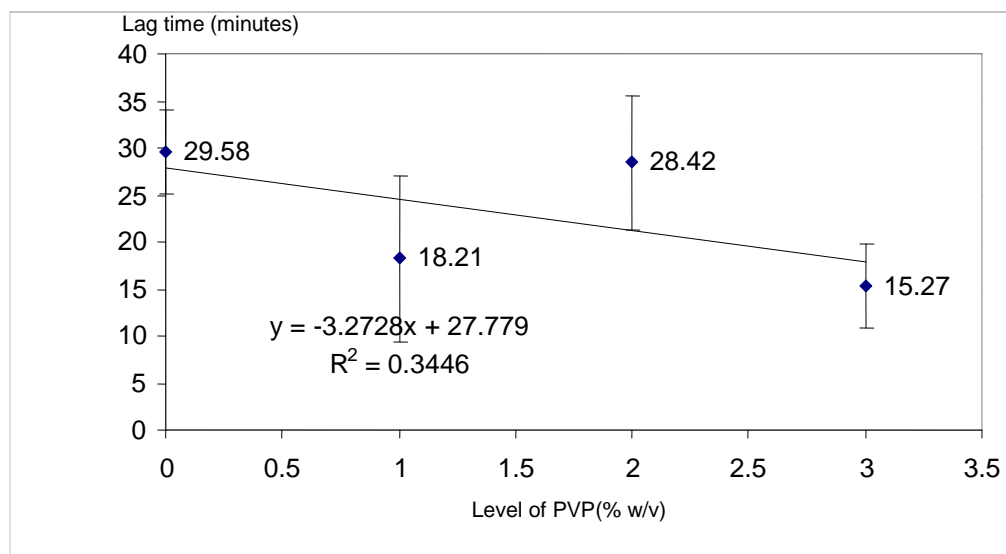


Figure 4. Relationship curve between levels of PVP with a latency time (lag time)

Increased levels of added PVP was not linier with the increase in cumulative amount absorbed significantly piroxicam. The study suggested is to use an aqueous suspension of piroxicam were added PVP, so that it can be seen more clearly the effect of adding to the absorption of piroxicam solubility.

Based on Fick law, permeability is affected by the diffusion coefficient, partition coefficient, surface area, and a thick membrane. Thick membrane ignored in this study because it is considered equal to the effective length of the colon 7 cm, so that the permeability is affected by the diffusion

coefficient and partition coefficient alone.

The diffusion coefficient is influenced by temperature, pressure, solvent properties, and chemical properties of difusan. Diffusivity depends also on the obstacles on the course of the diffusing molecules. Factors that influence is considered fixed, thereby influence the diffusion coefficient can be ignored because it is assumed constant (Martin *et al.*, 1983).

The partition coefficient is the ratio between the concentration of the drug in the lipid and drug concentration in the water. The addition of PVP is expected to

increase the solubility of the drug. However, because the total drug that is in the mucosal fluid is fixed, then the influence of the partition coefficient is the increase in the number of drug attachment on the surface of the membrane that are lipophilic.

Diffusion coefficient and partition coefficient is fixed so that the permeability of the membrane is fixed. PVP is also increased the membrane permeability of piroxicam but not linier with increased level of PVP.

Latent period is influenced by a thick membrane and diffusion coefficient of the intestinal wall, according to the equation 9. While the thick membrane is assumed fixed and rising levels of PVP does not affect the price of the diffusion coefficient of the price of the latent period is fixed. This study showed increased levels of PVP does not affect the latency time significantly. Similar research has been done using piroxicam with added PVP in solid dispersion (Patel *et al.*, 2003). The study indicates that the addition of PVP significant effect on the

increase in absorption of piroxicam compared with no addition of PVP. The present study indicates that the addition of PVP no significant effect on the increase in absorption of piroxicam compared with no addition of PVP. This study used a sample in solution, while Patel's study used a sample in the form of a solid dispersion.

The use of samples in the form of a solution less describe the effect of the addition of PVP which serves as an adjuvant because the solubility of piroxicam samples both with and without the addition of the addition of PVP was late so that the amount of drug absorbed was not significantly different. The use of samples in the form of a solid dispersion further illustrate the effect of the addition of PVP due to the interaction between solids piroxicam with PVP solids will form a complex which is more soluble in gastrointestinal fluids compared with pure piroxicam. PVP is more polar so easily soluble in water. Interaction with PVP piroxicam piroxicam polarity will result in increased, thus

increasing the solubility of piroxicam.

CONCLUSION

Lower doses of the surfactant (1%, 2%, and 3% PVP) significantly increased absorption of the drug absorption rate, and membrane permeability. But increased level of PVP have not linearity with the increased of drug absorption rate and membrane permeability.

ACKNOWLEDGMENTS

The authors wish to thank Gadjah Mada University and Sebelas Maret University that supported this work.

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